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## **Familial impairment of vocal cord mobility in childhood with clubfoot**

### **Running head: Congenital vocal cord immobility with clubfoot**

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## **Conflicts of Interest**

None of the authors report any conflicts of interest related to the research presented in this paper.

## **Abstract**

We report a family with three siblings, male and female, affected by congenital bilateral limitation of vocal cord abduction, with the additional finding of clubfeet in two. The paternal family history suggests autosomal dominant inheritance. The siblings and father also have mild craniofacial features, which may be an expression of variability or may be unrelated. The association of congenital vocal cord paralysis and clubfeet has been reported with additional major features or in the context of Charcot-Marie-Tooth disease. However, the two in isolation has been reported in only one other family previously. Genomic analyses of the family, including chromosomal microarray and exome sequencing, revealed neither a likely pathogenic variant in a known disease gene nor a compelling candidate gene variant. We propose the association of these two findings constitute a novel recognizable phenotype, for which a genetic cause remains undetermined.

**Keywords**

Vocal cord paralysis, vocal cord paresis, clubfeet, equinovarus deformity, familial, syndrome

**Introduction**

Impaired vocal cord movement can result in severe respiratory distress, swallowing difficulties, and dysphonia. It is the second most common cause of upper airway obstruction in infants, following laryngomalacia (Bonsal, 2012). Vocal cord immobility is most often a paralysis caused by abnormal or disrupted innervation, and less commonly is due to an anatomic anomaly such as cricoarytenoid joint fixation (Hillel et al., 1999). About half the cases of vocal cord paralysis are bilateral (versus unilateral) (Graham et al., 2007). Unilateral cases most commonly occurs as a result of traumatic surgical injury to the left recurrent laryngeal nerve (Graham et al., 2007). In contrast, most cases of bilateral VCP are idiopathic. Murty et al. (1994) estimated that only 0.75 per million infants per year are affected with bilateral vocal cord paralysis, a figure which includes paralysis due to damage to the innervation of the cords, idiopathic cause and genetic origin. Familial bilateral vocal cord immobility appears to be extremely rare, and specific genetic causes for most of these families have not been forthcoming. While chromosomal rearrangements have been suggestive as causative or predisposing in a very few families (eg., Hsu et al., 2014), specific genetic causes for most have not been forthcoming (eg., Tarin et al., 2005). In contrast, congenital bilateral clubfoot is a relatively common congenital anomaly, occurring in approximately one of every thousand live births in non-Hispanic whites (Parker et al., 2009). Most often, it occurs as an isolated malformation from multifactorial causation, but it can also be a feature of hundreds of genetic syndromes.

We present a non-consanguineous family of European descent with three siblings affected with congenital impaired vocal cord mobility, two of whom also have congenital bilateral clubfoot. Based on a reported history of hoarseness during infancy in the father and uncle, an autosomal dominant mode of inheritance is suspected, but other modes cannot be ruled out. We hypothesize that both the vocal cord immobility and clubfoot seen in this family are secondary to mutation of a gene involved in embryonic neuromuscular development.

## **Clinical Report**

### II.1 Sibling 1

The proband is a 12-year-old boy born at term after a pregnancy complicated only by mild gestational diabetes. An ultrasound at 23 weeks gestation was normal. Apgar scores were 3 and 7 at one and five minutes, respectively. Bilaterally clubbed feet were noted. He was intubated for severe respiratory distress and diagnosed with bilateral vocal cord immobility and mild laryngomalacia by flexible bronchoscopy at three days. He was successfully extubated four weeks later with significant improvement in vocal cord motility, although he remained stridorous after extubation when distressed. Stridor then resolved at approximately three months. At 7 years of age, vocal cord abduction was still limited to 20 degrees and adduction was full. Since infancy, symptoms of respiratory distress have only occurred with bouts of bronchitis, one requiring hospitalization at age 9 years. At present, he has a mildly high-pitched and hoarse voice. He reports he is unable to play wind instruments due to breathing difficulties and has been prescribed an inhaled bronchodilator, which he uses sporadically.

Sibling 1's bilateral equinovarus deformity was successfully treated with casting and manipulation. Initially, he showed mild weakness of the anterolateral compartments of the lower leg and femoral retroversion, but his power has improved into the normal range. A neurological

examination showed normal tone, normal deep tendon reflexes, down-going plantar responses, and normal gait. He has micrognathia (Fig. 1C), a highly arched palate, protruding ears, mild right eye ptosis, small palpebral fissures, low anterior hairline with frontal upsweep, and borderline microcephaly of 50 centimeters at six years (2<sup>nd</sup> percentile), which is out of keeping with parental head circumferences (50 – 75<sup>th</sup> percentile for mother and 75<sup>th</sup> – 90<sup>th</sup> percentile for father). Apart from delays and difficulties with both fine and gross motor skills, neurodevelopment has been normal and academic performance has been good.

An initial ophthalmology assessment in the newborn period showed no abnormalities, but at 12 weeks, a repeated eye exam noted mild right optic nerve pallor, variable right exotropia, and suspected nystagmus on the right side. By six months of age, bilateral horizontal nystagmus had become much more pronounced. In addition to bilateral optic nerve pallor, worse on the right than left, the retinal vessels were suspected to be narrowed. CT and MRI scans of the brain at six days of age had shown a tiny left cerebellar intraparenchymal bleed and scattered extra axial hematomas, most prominently in the left sylvian fissure. The cerebellar hemorrhage was queried as a contributing factor for the nystagmus initially, but then a family history emerged of nystagmus affecting a maternal cousin once removed and the maternal grandfather. His mother has a left esotropia. At 7 years of age, Sibling 1 had uncorrected visual acuity of 20 / 400 OD and 20 / 40 OS. A repeat brain MRI at age 9 years was normal apart from slightly small optic nerves. Table 1 summarizes findings in the proband and family.

## II.2 Sibling 2

Sibling 2 is a five-year-old girl born at term after a pregnancy with normal fetal ultrasounds, complicated only by gestational diabetes. A fetal ultrasound was normal in the

second trimester. At birth, Apgar scores were 8 and 8 at one and five minutes respectively, and respiratory distress was apparent. On the third day of life she was transferred to an intensive care unit for observation because of persistent stridor and hypoxic episodes, but invasive ventilation was not required. She was diagnosed with poor vocal cord mobility via laryngoscopy at four days of age. At four months, vocal cords were noted to abduct approximately 15 degrees, about half of expected. She shares the feature of protruding ears with her brother, but has greater growth of the mandible without frank micrognathia (Fig. 1D). She has a normal head circumference of 46.2 cm at 30 months of age (10<sup>th</sup>%ile). Sibling 2 does not have clubfoot. She has normal development and intellect. At two and a half years old, she continued to experience occasional stridorous episodes and was treated once with steroids for croup. She had a normal ophthalmology assessment.

#### II.4 Sibling 4

After the intervening birth of an unaffected girl, Sibling 3 (Fig. 2), Sibling 4 was born at term in a pregnancy again complicated by mild, diet-controlled gestational diabetes. No anomalies were noted on a second trimester fetal ultrasound. At birth her APGAR scores were recorded as 9 and 9 at one and five minutes respectively. She was admitted to hospital at four weeks of age for respiratory distress and was noted to have inspiratory stridor that was worse with crying but quieter when sleeping. The stridor did not affect feeding and no true cyanotic episodes occurred. She was diagnosed with impaired vocal cord mobility with less than ten percent movement. She was noted to have virtually no abduction capacity but was able to adduct her vocal cords sufficiently. She also had bilateral clubfoot, protruding ears, mild micrognathia, and mild laryngomalacia. Neurodevelopment has been normal. Her neurological examination was normal. She has ongoing intermittent aspiration of thin liquid, confirmed on a feeding study.

## I.2 and I.3

The family history was negative for confirmed vocal cord paralysis, and both mother and father had normal vocal cord motility (per laryngoscopy) at ages 30 and 32 years, respectively. However, the father (I.2) was reported to have had feeding difficulty as an infant and a “hoarse cry.” He had a large, benign congenital melanocytic nevus removed from his right thigh when he was 14 years old. Insulin-dependent diabetes was diagnosed at age 27 years, and both of his parents have adult-onset diabetes. He has micrognathia, mildly protruding ears and short palpebral fissures (Fig. 1). The father’s brother (I.3) was also reported to have a hoarse cry as an infant, which was not investigated. This man’s medical records mention mild, self-limited respiratory distress in the newborn period, and he shares the distinctive features of micrognathia and protruding ears. In early childhood, he had been followed for failure to thrive (or possible constitutional growth delay), which resolved by age 5 years. His height and weight were at the third centile in early childhood. He was unable to swallow any solid food without choking until 8 months of age. He was noted at age 14 years to have contractures of both hips causing external rotation.

## **Genomic analyses**

Sibling 1 had normal results from karyotype, chromosomal microarray (Affymetrix genome-wide SNP array 6.0), and *MYCN* gene sequencing and deletion / duplication analysis (to rule out Feingold syndrome [MIM# 164280] in view of the craniofacial features, plus a rare association with vocal cord paralysis). On a research basis, with written, informed consent (University of British Columbia protocol H09-01228), the family underwent exome sequencing of the father and all siblings. The sequencing for the father and siblings 3 and 4 was performed on an Illumina HiSeq2000 platform at MacroGen, Inc. with capture via the Agilent SureSelect V4 kit (51 Mb),



and the sequencing for siblings 1 and 2 was performed at Axeq Technologies. MacroGen performed the read alignment and variant calling using the Burrows Wheeler Alignment tool (BWA) and the genome analysis toolkit (GATK). Axeq also captured target regions with SureSelect and aligned Illumina reads with BWA and detected variants with SamTools. Variant annotation and analysis was performed with VarSeq software (Golden Helix). At least 92 - 96% of coding regions were covered by at least 10-fold read depth.

Segregation analyses of variants were performed under the following hypotheses: 1) autosomal dominant, inherited from father, absent in unaffected sibling; 2) autosomal dominant, inherited from father, unaffected sibling non-penetrant but mutation positive; 3) autosomal dominant, de novo in affected siblings from presumed gonadal mosaic parent; and 4) autosomal recessive in affected siblings. None of these analyses yielded either a likely pathogenic variant(s) in a known disease gene or a compelling candidate variant in a novel disease gene. Stringent scenario 1, after filtering for protein-altering variants with minor allele frequency <0.1%, yielded 12 variants, all of which were present at least 4 times in the gnomAD dataset of ~120,000 individuals lacking significant pediatric onset disease. The filter for allele frequency was relaxed to 0.5% for the autosomal recessive analysis, and there were no genes with bi-allelic variants shared among the affected siblings.

## **Discussion**

We report a family affected by impaired vocal cord mobility in early childhood with minor craniofacial findings, and variable presence of clubfeet. Of note, there is no other suggestion of cranial nerve dysfunction apart from unilateral ptosis in sibling 1. The father and paternal uncle share the craniofacial phenotype, and have historical reports suggestive of vocal cord impairment in early childhood, but the latter cannot be confirmed. Therefore, the mode of

inheritance is unclear albeit suggestive of autosomal dominance. It is important to consider that congenital vocal cord paralysis usually improves over time (Murty et al., 1994), and hence the father and mother's normal laryngoscopy findings do not necessarily establish them as unaffected.

Considering the lack of any morphologic anomaly observed with laryngoscopy, a neurological paresis seems more likely than an anatomic cause. However, EMG studies were not performed to confirm this. Familial vocal cord paralysis is extremely rare [laryngeal abductor paralysis, OMIM <sup>1</sup>150260 and 308850; see Abdelhalim et al. (2011) for a review]. A majority of familial reports have featured autosomal dominant inheritance and about half of reports describe congenital onset. Those cases presenting later in childhood or adulthood tend to feature progressive neuropathy, primarily Charcot-Marie-Tooth disease, and rarely familial amyotrophic lateral sclerosis. At least 12 reports have described apparently isolated familial vocal cord paralysis.

In 1982, Morelli et al. reported a family with similar features to that described here. Seven members across three generations were affected with vocal cord paralysis, two of whom were also affected by bilateral clubfoot. In this family, the severity of the vocal cord paralysis was highly variable, with two of the family members dying of respiratory failure as a result of the vocal cord paralysis in early infancy, whereas other family members never required invasive intervention. Two family members required surgical intervention in young adulthood; little information was provided regarding respiratory / vocal symptoms prior to that. Peterson et al. (2014) reported a proband with some similar features to individual II.1 (clubfoot, vocal cord paralysis, midface hypoplasia, optic nerve hypoplasia, microcephaly) and a microduplication on 17q23 inclusive of 18 genes, of which TBX4 was suspected to be most responsible for at least the clubfoot based on a minimal-region analysis in other families. However, the proband had

additional findings, including heart defects, brain abnormalities, and hearing loss. The mother and a sister with this copy number variant were phenotypically normal, and a brother with it had clubfoot without any of the other associated abnormalities, suggesting reduced penetrance. It is unclear in this family whether both the vocal cord paralysis and clubfoot share the same etiology. Hawkins et al. (1990) described a family where a pair of identical twins presented at birth with bilateral abductor vocal cord paresis and finger deformities. The study also reported one other male sibling with stridor in infancy and digital abnormalities, a first cousin with vocal cord paralysis and finger abnormalities, and other family members with finger abnormalities in the absence of vocal cord dysfunction.

A third syndromic presentation, associated with a missense variant in TUBB3, variably comprised intellectual disability, microcephaly, Kallmann syndrome (hypogonadism and anosmia), ptosis and other cranial nerve palsy, tracheomalacia, vocal cord paralysis and progressive peripheral neuropathy (Chew, 2013).

Finally, congenital myasthenic syndrome secondary to DOK7 mutation was considered in this family because of the prominence of ptosis and congenital vocal cord paralysis in this rare condition, but the lack of progressive muscular weakness in this family makes this an unlikely diagnosis overall (Klein, 2013).

Bilateral vocal cord paralysis is usually idiopathic in origin, and though pathogenesis of the disorder is generally poorly understood, some theories have been postulated. Paralysis can occur due to lesions in the central nervous system such as Arnold-Chiari malformations, haemorrhage, hydrocephalus, myelomeningocele or hypoxic cerebral palsy (Nisa et al., 2012; King et al., 2011). An Arnold-Chiari malformation is characterized by herniation of the cerebellum and brainstem through the foramen magnum, and may directly or indirectly put

pressure on the vagus nerve, causing paresis of the recurrent laryngeal nerve and thereby affecting vocal cord function (King et al., 2011). Clinically silent subdural hematomas can cause vocal cord paralysis in a similar fashion (Alshammari et al. 2012). Delayed neurological maturation has also been proposed as a mechanism (Grundfast and Milmoe, 1982). This idea is supported by the remarkable improvement that usually ensues during early infancy, although simple increase in glottis airway diameter with growth might also account for the decrease in obstructive symptoms (Grundfast and Milmoe, 1982). Dysgenesis of the nucleus ambiguus has also been suggested as a possible etiology (Plott, 1964). In addition to these theories, insufficient chemoreceptor ventilator control reflex has been proposed, as well as impaired coordination of laryngeal stimulation (Abdelhalim and Vaccani, 2011). Alternatively, vocal cord paralysis could be the earliest manifestation of a progressive neurological disorder such as Charcot-Marie-Tooth disease or familial amyotrophic lateral sclerosis. Though vocal cord paralysis usually presents as a late symptom in these diseases, there are reports of vocal cord paralysis or respiratory distress appearing as the presenting symptom (Pehlivan et al., 2015; Origone, 2012; Hermann et al., 2011). The molecular pathogenesis of bilateral familial vocal cord paralysis in the absence of other abnormalities remains elusive, and may best be discerned according to known function of relevant genes.

In addition to congenital vocal cord dysmotility, Sibling 1 presents with nystagmus and optic nerve atrophy. This visual impairment is suspected to be secondary to a mild neonatal brain injury. There is an unconfirmed maternal family history of nystagmus and strabismus, whereas the vocal cord impairment in this family is thought to be more likely inherited paternally.

Regarding the craniofacial findings in this family, these features seem to segregate with the vocal cord paralysis in the siblings, and the unaffected daughter resembles her mother more,

whereas the affected siblings resemble their father who is also suspected to have been affected as a child. These craniofacial features include small palpebral fissures, ptosis, protruding ears, micrognathia, high arched palate, and small head circumference. In the literature, these features are not distinctly mentioned as previously occurring together with familial vocal cord paralysis; however, Schinzel et al. (1990) noted microcephaly with the variable presence of intellectual disability amongst affected family members. Koppel et al. (1996) reported a consanguineous family presenting with congenital vocal cord paralysis and a high arched palate in a single affected member. Ptosis was mentioned in two individuals with congenital bilateral vocal cord paralysis in another family (Tucker, 1938).

In conclusion, this family presents with a very rare phenotype including congenital bilateral vocal cord abductor limitation (not requiring tracheostomy), mild craniofacial features, and variable bilateral clubfoot. Further studies into the underlying genetic cause of this and other families with the same phenotypic features will hopefully provide insight into the physiological mechanism of the vocal cord paralysis.

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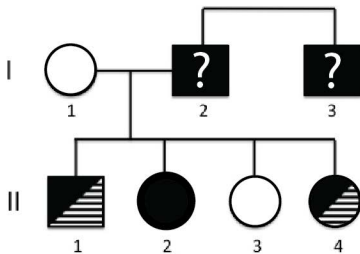
Figure 1. Facial photographs demonstrate micrognathia (A), short palpebral fissures (B), and prominent ears (B) in the father; micrognathia in sibling 1 (C), who also has short palpebral fissures and prominent ears; and a relatively well-formed mandible in sibling 2 (D). Photographs were unavailable for sibling 4.

Figure 2. Pedigree.

Table 1. Summary of phenotypes.

	Sibling 1	Sibling 2	Sibling 4	Father	Mother
<b>Vocal cord paralysis</b>	Bilateral	Bilateral	Bilateral	Suspected in childhood; now resolved	-
<b>Clubfoot</b>	Bilateral	-	Bilateral	-	-
<b>Head circumference At birth</b>	33.5 cm (42 <sup>nd</sup> %ile) 37 w 4 d	34.5 cm (44 <sup>th</sup> %ile) 40 w	34.5cm (50 <sup>th</sup> %ile) 38 w 5 d		
<b>Most recent</b>	50.2 cm (2 <sup>nd</sup> %ile) 8 years	46.2 cm (10 <sup>th</sup> %ile) 30 months	47 cm (25 <sup>th</sup> %ile) 30 months	(75 <sup>th</sup> - 95 <sup>th</sup> %ile)	(50 – 75 <sup>th</sup> %ile)
<b>Height</b>	127. cm (45 <sup>th</sup> %ile) age 8 years	73.2 cm (20 <sup>th</sup> %ile) 14 months	85 cm (5 <sup>th</sup> %ile) 30 months		
<b>Nystagmus</b>	+	-	-	-	-
<b>Optic nerve atrophy</b>	+ Possibly secondary to brain injury	-	-	-	-
<b>Ptosis</b>	Right eyelid	-	-	-	-
<b>Short palpebral fissures</b>	+	-	+	+	-
<b>Mild micrognathia</b>	+	-	+	+	-
<b>Prominent ears</b>	+	+	+	+	-





vocal cord paralysis



clubfoot



history of vocal cord paralysis uncertain